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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/311,428	O CONNOR ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Amendment Entry

1. Applicants' amendment-F filed in response to the Office Action mailed 19 November 2002 in Paper #22 is acknowledged. The disclosure along with claims 81-83 have been amended. Currently, claims 81-91 are pending and under consideration.

OBJECTIONS WITHDRAWN

Specification

Applicants amendments filed 24 March 2003 have obviated the following objections.

2. Applicant's will submit a corrected version of the paragraphs containing references to trademarks in due course. Until receipt of applicant's response the objections are maintained. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

3. The use of trademarks has been noted in this application (For example see "Superose" on page 12, line 18). They should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Superose has not been capitalized in the disclosure. The objection remains.

4. *The objections are withdrawn.*

OBJECTIONS MAINTAINED

Drawings

5. The drawings in this application have been objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner. Applicants have deferred revised drawing corrections until allowance of the instant application. The objection is maintained.

REJECTIONS WITHDRAWN

6. Rejections of record in paper #18 for reasons of record are withdrawn. The claims have been amended to recite an EPMI-hCG indicating early pregnancy associated molecular isoform of hCG (supported by the specification on page 32 lines 9-10).

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 81, 82 and 87-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a method of detecting gestational trophoblast malignancy via combinations of antibodies produces from hydriboma cell lines B152, B109, B108, and B207.

Therefore the written description is not commensurate in scope with the claims drawn to the utility of any two or three antibodies in combination to measure gestational trphoblast malignancy. Further because the claims merely read on the detection of an EPMI-hCG which is not clearly identified in the disclosure, there is no clear indication as to what is actually being measured. Due to the lack of written description of the structure or identity of the EPMI-hCG molecule, one cannot generate other antibodies to the specific EPMI-hCG molecule of the instantly claimed invention. Therein the specific antibodies disclosed in the specification are required to insure detection of the appropriate molecules having direct correlation to gestational trophoblast malignancy. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115). With the exception of antibodies produces from hydriboma cell lines B152, B109, B108, and B207, the skilled artisan cannot envision the detailed structure of the encompassed antibodies and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it.

The antibody itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of a compound/seq.id/etc. by only their functional activity does not provide an adequate written description of the genus. The court indicated that while

Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules, usually defined by a sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description ...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

However, no disclosure, other than antibodies produces from hydriboma cell lines B152, B109, B108, and B207 is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only methods utilizing the antibodies produced from hydriboma cell lines B152, B109, B108, and B207, but not any and all antibodies would meet the full breadth of the claims as required by the written description provision of 35 USC 112, first paragraph.

Response to Arguments

Applicant contends that the antibodies of the instant method are distinguished by their relative binding affinities for hCG isoforms. Specifically exemplifying B151 and B152 antibodies which distinguish C5 chorio hCG and nicked hCG as taught by the specification at page 76 through 77 and figure 12. This argument was carefully considered but not found persuasive because the cited claims do not describe distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention as required by MPEP 2163.02.

The instant antibodies are not identified by name (ie B151, B152) or by binding affinity (ie C5 chorio hCG and nicked hCG) in claims 81, 82 and 87-91. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Accordingly the rejection is maintained.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 81-91 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of US Patent #6,500,627 in view of El-Ahmady et al. (Anticancer Research, 1996, Vol.16, No. 4B, pages 2301-2308 – Abstract Only.

Although the conflicting claims are not identical, they are not patentably distinct from each other because The instant claims are not patentably distinct from the claims found in US Patent #6,500,627 because the claims employ the same method steps that encompass obvious modifications in assay design while utilizing the exact same reagents (i.e. molecular isoforms of hCG, non-nicked hCG, B152, B109, and B108). Although one preamble recites "A method of predicting pregnancy outcome – US Patent #6,500,627 " and the other preamble recites "A method of detecting gestational trophoblast malignancy – 09/311,428", the preambles encompass the same subject matter. The relationship of hCG in pregnancy, gestational (pregnancy related) trophoblastic and non-trophoblastic malignancies is supported in the Reference f El-Ahmady et al. See abstract.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 81-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellish et al. (Human Reproduction, 1996) in view of Krichevsky et al. (US Patent #6,339,143) and in further view of Price et al. (Journal of Clinical Endocrinology and Metabolism, 1996, Vol.81, No.3, pages 1160-1163).

Ellish et al. teach an immunoradiometric assay which has two solid-phase immobilized capture antibodies and one detection antibody to study early pregnancy loss.

Ellish et al. employ B109 to capture the non-nicked hCG molecule and B207 to capture free β subunit and hCG free β core fragment. Ellish et al. utilized B108 as the radioactive labeled detection antibody. (page 4074, column 2) .

Ellish et al differ from the instant invention in not teaching the utility of monoclonal antibody B152 is combination with other antibodies as an indicator of trophoblast malignancy.

Krichevsky et al. teach method and antibodies to measure hCG with respect to pregnancy. Column 3 lines 32-42 and lines 52-60 and column patent the utility of various antibodies including B152 in hCG binding is outlined. See figure 1. Monoclonal B151 and B152 preferentially binding only on nicked human chorionic gonadotropin. Monoclonal antibody B207 (instant claim 85) was also exemplified. Column 6 lines 33-41. Antibody measurements and ratios are further taught as useful in evaluating the fetus (ie Down's Syndrome). Column 10 lines 10-38. The method is also utilized to determine malignant tumors. Krichevsky et al. disclose hCG as a glycoprotein hormone produced by the trophoblast early in pregnancy. Column 24 lines 18-20. Accordingly the detection of hCG would identify the trophoblast malignancies.

Although Krichevsky et al. employ the same antibody as the instant invention (B152 in claim 83), they do not specifically recite that B152 can measurement EPMI (isoforms of hCG) as an indication of a gestational trophoblast malignancy. With respect to B152 binding EPMI-hCG, it has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138.

However, Price et al. have evaluated pregnant women for the increased risk of gestational throtoxicosis. Price et al. disclose that the genetic difference in the production and metabolism of hCG isoforms may account for the increased risk. See abstract. Therein teaching the importance of hCG isoforms in pregnancy assessment.

It would have been prima facie obvious to one of ordinary skill in the art to utilized the multiple antibody method of Ellish et al. include antibody B152 of Krichevsky et al. to evaluate hCG isoforms in a gestational malignancy as taught by Price et al. because Krichevsky et al. taught that antibody B152 [distinctively] binds to an epitope present only on nicked human chorionic gonadotropin (column 6 lines 33-37) while, Price taught that various forms of hCG including the isoforms play an important role in pregnancy. Price et al. show that hCG isoforms such as asialo hCG were elevated in gestational thyrotoxicosis, when intact hCG and FT_4 levels were not. See page 1162, 2nd column.

One of ordinary skill in the art would have been motivated to measure hCG isoforms as well as the other forms of hCG in order to completely evaluate pregnancy disorders. Therein accounting for disorders which cause elevation in only the isoforms of hCG.

11. For reasons aforementioned, no claims are allowed.

Remarks

12. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

I. Birken et al. (Endocrinology 1993) disclose a two-site immunoradiometric assay to evaluate immunopotency of nicked hCG. Birken et al. further teach a capture antibody that specifically binds non-nicked hCG (intact hCG heterodimer) along with a detecting (tracer) antibody. The capture antibody is B109 and the I125 radiolabeling antibody is B108. (See page 1391, column 1).

II. O'Connor et al. (Cancer Research, 1988) disclosed assays to evaluate hCG function. O'Connor et al. specifically teach immobilized capture antibodies via B108 or B109 coated solid phase materials which specifically bind non-nicked hCG. (See page 1362, column 1).

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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